Case Report

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The Blue Rubber Bleb Nevus Syndrome: A Delayed Diagnosis Made Possible by Video-Capsule Endoscopy. Case Report and Review of the Literature

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ABSTRACT

Blue rubber bleb nevus syndrome (BRBNS) is a rare, severe, sporadically occurring disorder characterized by multiple venous malformations. The most common clinical presentation is symptomatic anemia due to GI bleeding, both overt and occult. The present study reports a 15-year-old female with iron-deficiency anemia refractory to therapy. She underwent various unsuccessful investigations to find the origin of the anemia.

We only belatedly reached a diagnosis based on video-capsule endoscopy (VCE) findings. Cutaneous vascular malformations and multiple hemangiomas in the stomach and the small bowel revealed by endoscopy led to the diagnosis of BRBNS. We should consider VCE as a diagnostic modality for suspected GI vascular malformations in children.

Keywords: Blue Rubber Bleb Nevus Syndrome; Occult Blood Loss; GI Bleeding, Capsule Endoscopy

Abbreviations: BRBNS: Blue Rubber Bleb Nevus Syndrome; VCE: Video-Capsule Endoscopy; GI: Gastrointestinal; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; IDA: Iron-Deficiency Refractory Anemia; mTOR: Mammalian Target of Rapamycin; PI3K: Phosphoinositide-3-Kinase; IBD: Inflammatory Bowel Disease; OGIB: Obscure Gastrointestinal Bleeding

Introduction

Blue rubber bleb nevus syndrome (BRBNS) or Bean Syndrome is a rare congenital disorder presenting with multifocal venous malformations of the skin, soft tissue, and gastrointestinal (GI) tract. This condition was first described in 1860 by Gascoyen [1]. In 1958, Bean attached the label blue rubber bleb nevus syndrome to this rare condition because of the characteristic presence of skin lesions [2]. Gastrointestinal tract involvement is the most common feature, leading to concerns for possible bleeding, potential chronic occult blood loss, and iron deficiency anemia. Hemangiomas may also appear in other body areas, including the eye, central nervous system, liver, spleen, thyroid, parotids, kidney, bladder, and skeletal muscles [3]. The syndrome is rare, with an incidence rate of 1:14,000 and only approximately 200 cases reported [4]. There is no consensus in the literature to indicate increased prevalence according to race or sex, but it seems rare among black subjects [5].

BRBNS is usually a sporadic disorder; however, autosomal dominant modes of inheritance are reported, specifically with a locus found on chromosome 9p.

The diagnosis of BRBNS is challenging due to the rareness of the syndrome and the variability in clinical presentation. Most patients with BRBNS are diagnosed at birth or during early infancy (30% since birth, 9% in preschool age, 48% in infancy, 9% in adolescence,

and 4% in adulthood) [6]. Patients may have multiple venous malformations, appearing as blue soft compressible nodules on the skin or mucous membranes. They are often born with a «dominant» lesion and develop numerous «satellite» venous malformations over their lifetime [7]. The typical skin lesions are described as rubbery in consistency and may be painful or tender when compressed. These lesions can range from only a few millimeters to up to 4 to 5 cm in diameter. They can grow over time, and more lesions may develop in the skin or gastrointestinal tract. Significant and disfiguring blue marks may appear, as well. Uniquely, lesions tend to swell in gravity-dependent positions, and patients have focal areas of hyperhidrosis overlying them [8]. Venous malformations are slow-flow lesions, making them prone to thrombosis that presents as an erythematous, warm, and tender swelling [9]. Other venous malformations can be seen throughout the body (heart, spleen, liver, central nervous system, and gastrointestinal tract). The small bowel is the most common site of gastrointestinal (GI) tract involvement; however, lesions can occur anywhere from the mouth to the anus [10]. GI BRBNS's primary clinical manifestation is acute or chronic bleeding [8]. The diagnosis of BRBNS is established based on characteristic cutaneous lesions, with or without GI bleeding, and the involvement of other organs. Essential evaluation of patients should include a complete history and physical examination, blood count, and fecal occult blood test to detect anemia and GI bleeding [11].

The diagnostic workup includes an x-ray, CT, MRI, and endoscopy. Abdominal radiography may show phlebitis of thrombotic intestinal lesions. Computed tomography (CT) and magnetic resonance imaging (MRI) can determine where other hemangiomas may have developed within the body [12]. The advantage of these two modalities is the ability to display large portions of the body. Visualization and assessment of hemangiomas within the GI system occur by esophagogastroduodenoscopy, colonoscopy, video-capsule endoscopy, and other minimally invasive procedures that combine surgery and endoscopy [13,14]. The prognosis of BRBNS depends on the location, the extent of the disease, the organs involved, and the need for aggressive treatment [8]. GI lesions severely affect the prognosis and pose the most significant management difficulties in obtaining adequate and lasting results with minimally invasive procedures. Cutaneous lesions occurring in high-risk traumatic areas or joints usually require treatment to avoid bleeding: surgery, sclerotherapy, or laser photocoagulation have been proposed as possible approaches [9]. This paper aims to describe a pediatric case of BRBNS, with cutaneous and small bowel involvement, underlying the management challenges and the usefulness of video-capsule endoscopy in detecting vascular lesions and obtaining a definitive diagnosis.

Case Report

In March 2022, a 15-year-old female came to our attention with iron-deficiency refractory anemia (IDA), manifesting as pallor, fatigue, and poor exercise tolerance. According to laboratory examinations, the patient exhibited a hemoglobin level of 11.4 g/L, a red blood cell counts of 5.88/mm3, a typical white blood cells count, and increased neutrophil granulocytes. Blood pressure and heart rate were normal. At birth, she partially removed a venous malformation of the left paravertebral region without diagnosing congenital vascular syndrome. From the age of 9 years, she underwent iron supplementation, and she received multiple blood transfusions. She never reported GI bleeding (melena or hematochezia), abdominal pain, diarrhea, and significant weight loss. The patient had no history of non-steroidal anti-inflammatory drug use or peptic ulcers. She underwent various investigations for IDA assessment, including abdominal CT and technetium-99m-pertechnetate scan with normal findings. At our Surgical Department, a rubbery cutaneous venous malformation under the left sole and a blue vascular papule over the right palm were noticed. Both lesions appeared at the age of 6 years. They were deep-blue, soft, rubbery, easily compressible, and painful (Figure 1).

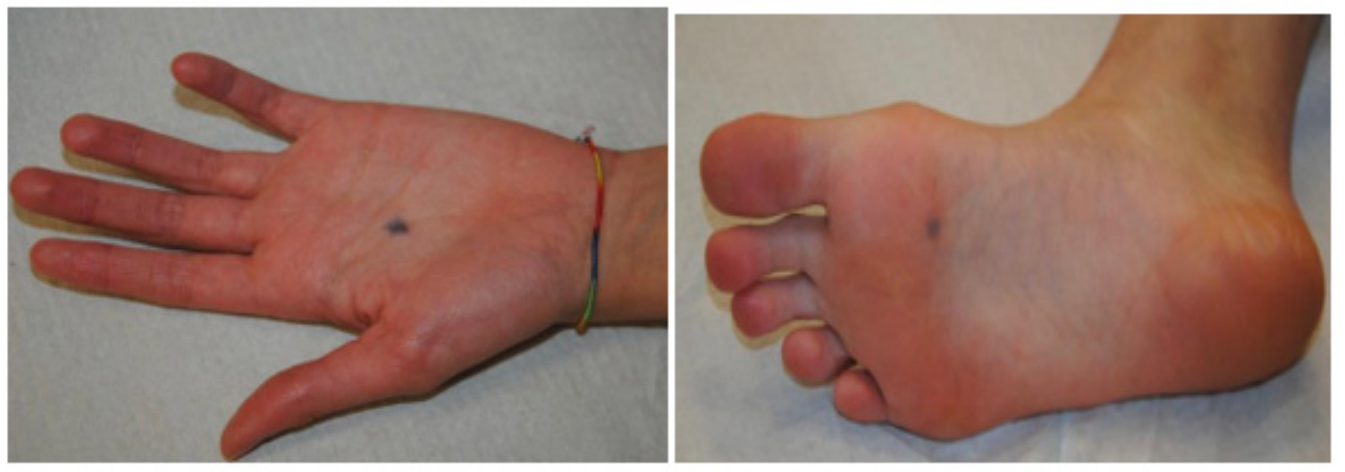

Figure 1: Vascular malformations on the patient's palm and sole.

The upper gastrointestinal endoscopy revealed two strawberry-like mucosal polypoid lesions in the stomach. The lesions ranged between 10 and 20 mm and appeared blue-violet and sessile.

A few days later, considering the medical history of the patient (particularly the removal of a vascular malformation in early infancy), the presence of cutaneous vascular lesions, and the endoscopic findings, together with the precarious clinical picture, we decided to explore the lower GI tract, as well. Therefore, the girl was a candidate for Video-Capsule endoscopy (VCE). No gastroscopic assistance for capsule introduction was needed, as she quickly swallowed the device after proper intestinal preparation. VCE disclosed more than ten hemangiomas distributed evenly in the small bowel (Figure 2). No lesions were detected in the colon and rectum. We established the diagnosis of BRBNS based on clinical history, the characteristic physical appearance of the cutaneous lesions, and the pathognomonic endoscopic appearance of the gastrointestinal lesions. The histopathological examination of these lesions confirmed the diagnosis of hemangiomas. We adopted a conservative medical approach: oral iron supplementation for the anemia and long-term Sirolimus treatment to obtain clinical remission. Sirolimus is an immunosuppressant drug that has both antiangiogenic and antineoplastic properties. Its mechanism of action is via pathway inhibition of the mammalian target of rapamycin (mTOR), a serine/threonine kinase regulated by phosphoinositide-3-kinase (PI3K) [15]. The treatment with Sirolimus was initiated and slowly increased to an oral dose of 0.1-0.15 mg/kg/die to maintain serum levels of 8-10 ng/mL. In three months, hemoglobin levels normalized without requiring further blood transfusions. We observed no adverse effects. We followed our patient monthly, with periodic evaluation of sirolimus blood levels and laboratory tests (complete blood cell count, analysis of plasma proteins, and lipid status). The patient is still on sirolimus, and we plan to continue the therapy for a year and then repeat the endoscopic examination.

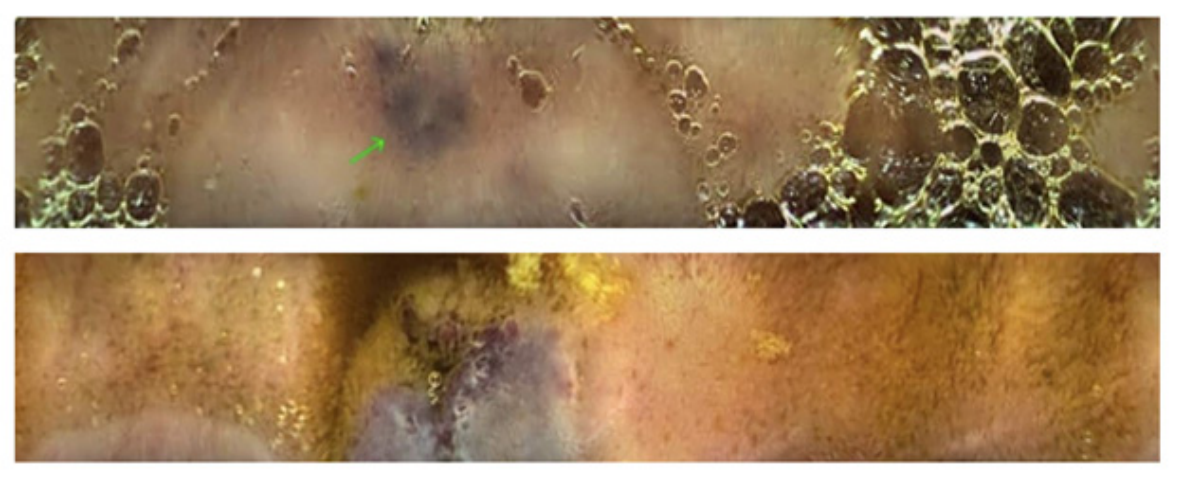

Figure 2: At VCE, we observed multiple hemangiomas of different sizes throughout the small bowel.

Discussion

We reported a rare case of BRBNS with delayed diagnosis due to fragmented and prolonged management with poor consideration of the initial treatment path, specifically removing a vascular malformation. At first, the girl was evaluated for an aggressive form of iron-deficiency anemia (IDA) refractory to medical treatment. She never reported macroscopic GI tract bleeding, leading physicians to delay the referral to a pediatric center with gastroenterological, surgical, and endoscopic expertise. Anemia is a frequent condition (IDA prevalence is 9.6%) and represents a diagnostic challenge during childhood [16]. GI causes of IDA are well-known (e.g., H. Pylori infection, coeliac disease, inflammatory bowel disease, and, anecdotally reported, autoimmune/collagenous gastritis, post-surgical conditions, vascular malformations, BRBNS), but the evidence is poor in defining their true incidence [17]. Therefore, evidence regarding endoscopy in pediatric IDA remains scarce. In 2019, experts recommended upper GI endoscopy for pediatric chronic refractory anemia of unknown origin [17]. Lower GI endoscopy should be considered in the diagnostic process and VCE in cases of persistent anemia and inconclusive procedures, with or without device-assisted enteroscopy [17]. VCE inspects the GI below the horizontal part of the duodenum, jejunum, and ileum. VCE was approved for use in children over two years of age by the US FDA in 2009 and ESGE in 2016 [18,19]. The most frequent indications for VCE in children are inflammatory bowel disease (IBD), obscure gastrointestinal bleeding (OGIB), malabsorption, protein-losing enteropathies, abdominal pain, small bowel polyps, and tumors [20]. In patients with obscure bleeding, its overall accuracy is high (91.1%), as well as its sensitivity (88,9%), specificity (95%), and positive predictive value (97%) [21].

On the other hand, in case of manifest GI bleeding, upper and lower GI endoscopies are universally accepted as standard procedures, as stated in the ESPGHAN guidelines and other papers [18,22,23].

GI lesions in BRBNS may appear throughout the GI tract, most often in the small bowel and distal colon, with different clinical and endoscopic manifestations: they may appear as strawberry-like mucosal polyps, submucosal protrusions, polylobulated, nodular, sessile, pedunculated or ulcerated lesions. Ulcerations usually determine acute bleeding presenting as hematemesis, melena, or rectal bleeding but may also lead to occult chronic GI bleeding. Anemia in BRBNS could become very disabling, requiring lifelong treatment with iron and blood transfusions. The potential anemia risks push doctors to perform timely diagnoses and think of possible definitive therapies. VCE should be considered a simple and non-invasive diagnostic tool for GI BRBNS. Several endoscopic therapeutic procedures (depending on the severity of the clinical presentation) are available for bleeding BRBNS: bipolar electrocoagulation, elastic ligation band, and polypectomy technique by diathermic snare laser, Nd: YAG (neodymium: yttrium-aluminum-garnet laser) therapy, plasma argon coagulation [24,25]. However, a conservative approach or a limited treatment is preferred for the known risk of recurrences and the low incidence of complications.

GI complications of BRBNS, such as volvulus, intussusception, and intestinal infarction, are infrequent and malignant transformations have not been reported so far [8,26]. For these reasons, some authors recommend conservative endoscopic follow-up avoiding operative procedures in case of stable lesions [25]. However, the rarity of this condition in children and the need for papers investigating GI BRBNS determine low levels of evidence in delineating specific management, starting from the diagnostic work-up. In particular, only a few studies describe the usefulness of VCE in evaluating the digestive involvement in pediatric patients with BRBNS.

Table 1: Literature review of pediatric BRBNS in the last five years.

Reference First Author, Year	Age (Y) / Gender	Main Vascular Lesions		Additional Lesions			Management After BRBNS Diagnosis	Follow-Up (Length)
		Type of Lesions	Symptoms	First Evaluation and Findings	Final Evaluations D: diagnostic delay	VCE Timing (T) and findings (F)		
[27]	15 / F	Cutaneous nodules on right opisthenar (resected at six months old)	Refractory IDA	Abdominal and thorax CT: negative Upper GI: gastric and duodenal mucosal erosions and duodenal mass Lower GI: rectal sessile polyp located	ND	(T) After GI evaluation (F) Dozens of blue vascular blebs (0.4 to 1 cm) from the jejunum to the ileum, and active bleeding in an ileal segment	Ileal lesions resection and iron suplementation for 3 months supplementation for 3 months	Anemia resolution (3 years)
[28]	16 / M	Blue-black nodules that gradually appeared and elarged on his back and extremities since the age of 3 years	IDA and pubertal delay	US and CT: cystic masses on the chest wall, back, and buttock. Upper and lower GI: multiple scattered bluish-to-purplish venous malformations throughout the entire GI tract	(D) 7 years history of IDA	No	Conservative: iron supplementation	ND
[29]	18 / M	Blue nevus-like lesions on the lip and the foot	Body hair impaired growth and erectile dysfunction	CT scan: adrenal venous angioma with calcifications, gastric polypoidal and colon soft lesion	No	No	ND	ND
[30]	18 / M	Multiple cutaneous venous malformations from the age of 10 months	Severe IDA and hematochezia	MRI (3-year-old): multiple hepatic and GI VMs RBCT GI lesions resection (6-ear-old)	Upper GI: multiple submucosal vascular malformations (D) 15 years	No	Sirolimus (> 12 months)	Recovered with Sirolimus

[31]	13 / M	At birth, right foot hemangioma resected at two years old	IDA and melena	RBCT	Upper and Lower GI: negative (13-year-old) (D) 10 years	(T) 10 years after symptom onset (F) Multifocal hemangioma-like purplish blue lesions in jejunum and ileum	Endoscopic treatment (Single-balloon enteroscopy)	Good clinical condition (1 year)
[32]	9 / M	At the age of 1, venous malformation in the knee	GI bleeding	Upper and lower GI: several typical blue lesions in the stomach, small bowel and colon	No	(T) With other endoscopic evaluations (F) Several blue lesions in small bowel and colon	Endoscopic treatment (argon plasma coagulation and sclerotherapy	Any new bleeding
[33]	10 / F	No	IDA	Upper and lower GI: negative	No delay	(T) With other endoscopic evaluations (F) Dark and red-colored submucosal tumor in the third portion of the duodenum	Endoscopic treatment	Recovered (3 months)
[34]	2 / F	At birth: cervical subcutaneous tumor with papulonodular blueish lesions	Recurrent GI bleeding	Cervical US and MRI at birth multiple RBCT	Total body MRI and upper and lower GI: numerous VMs, from the gastric to the intestinal and colonic mucosa (D) 2 years	No	Sirolimus (2-year-old) Resections of an intra-articular VM and of a subcutaneous lesion (8-year-old)	Stable (10 years)
[35]	17 / M	Dark, soft blue lesions on the shoulder	IDA	Conservative with RCBT	Upper and lower GI: vascular lesions VCE No delay	(T) With other endoscopic evaluations, 1 year after symptom onset. (F) Sessile venous lesions in the small intestine.	Single-balloon enteroscopy-assisted laparoscopy and resections.	Asymptomatic (6 months)
[36]	17 / F	Lower hip blue nevus	IDA	Lower GI: cecal angiodysplasia	Brain-MRI AbdominalUS	No	Conservative: supplementation of iron, folic acid and valproic acid	No need for transfusions (1 year)
[37]	38-days old / F	Multiple skin lesions	IDA and hematochezia	Abdominal CT: hepatic multiple lesions	No delay	No	Conservative: sirolimus	Resolution of anemia and lesions regression (2 years)
[38]	4 / F	Several vascular skin lesions (lumbar region, left thigh, forearm, and on the sole of the right foot)	Chronic GI bleeding, IDA	US: hepatic, pancreatic, vescical, ovarian vascular malformations.	No delay	(T) With other endoscopic evaluations (F) Sessile venous lesions in the small intestine.	Multiple sclerotherapy (antegrade and retrograde access)	Recurrent anemia after 15 months (sclerotherapy)

[39]	8 / F 9 / M 5 / F 11 / F	All patients with diffuse cutaneous distribution and clubbing-like digital thickening	ND	ND	ND	ND	ND	ND
[40]	18 / M	Cutaneous lesions, lungs, adrenal glands, GI tract	IDA	RBCT	ND	ND	Endoscopic treatment (sclerotherapy + APC) Sirolimus (> 12 months)	Mouth ulcer and acne
	8 / F	Cutaneous lesions, lungs, liver, mesentery, GI tract	IDA	RBCT	ND	ND	Endoscopic treatment (sclerotherapy + APC) Sirolimus (> 12 months)	Mouth ulcer
	15 / F	Cutaneous lesions, tongue, lung, liver, adrenal glands, vaginal wall, GI tract	IDA	RBCT	ND	ND	Sirolimus (> 12 months)	Mouth ulcer and acne
	4 / F	Cutaneous lesions, tongue, liver, GI tract	IDA	Endoscopic treatment (sclerotherapy)	ND	ND	RBCT Sirolimus (> 12 months)	Mouth ulcer
	5 / F	Cutaneous lesions, GI tract, paraspinal muscles, tongue, lungs, liver, adrenal glands, perineum	IDA	Endoscopic treatment (sclerotherapy) RBCT	ND	ND	Sirolimus (> 12 months)	Mouth ulcer
	9 / F	Cutaneous lesions, GI tract, hip joint, perineum	IDA	RBCT	ND	ND	Sirolimus (> 12 months)	Recovered
	5 / F	Cutaneous lesions, GI tract	IDA	RBCT Endoscopic treatment	ND	ND	Sirolimus (> 6 months)	Recovered
	5 / M	Cutaneous lesions, GI tract, lungs, liver, pelvic floor	IDA	RBCT	ND	ND	Sirolimus (< 6 months)	Mouth ulcer and elevated liver enzymes
[41]	1 week old / F	Multiple elevated deep-blue skin lesions on head, trunk, and limbs	None	MRI: multiple skin and soft tissue nodules in the lower trunk and extremities	No No delay	No	Conservative: sirolimus	Stable (3 years)
[42]	11 / F	Ear and thigh bluish lesions since birth	Progressive lesions growth and new lesions appearance	Doppler US: venous flow Cranial CT: cortical veins ectasia Upper and lower GI: no lesions	Dorsal lesion removal for histopathology (11-year-old)	No	Lesion removal to obtain diagnosis and differentiate from glomangiomas	ND

[43]	10 months / M	Multiple blush bleb papules, nodules ad swellings all over the body since birth	Motor development delay	Dermoscopy Lower limbs x-ray: increased girth of left thigh Doppler US: venolymphatic malformation Left thigh MRI: large venolymphatic malformation with intramuscular involvement	(D) 10 months	Not advised due to negative stool guaiac test	Compression stockings	ND
[44]	9 / M	Vascular malformation of knee, right lung	IDA	Upper and lower GI VCE Abdominal / chest CT angiography	No	(T) Upon arrival. (F) Ileal vascular malformation.	Conservative: sirolimus (1 year-long)	Resolution of bleeding and anemia
	7 / M	Neck vascular malformation (excised)	IDA (no GI bleeding)	Iron replacement therapy	Upper and lower GI (5 years): vascular lesions in the colon	No	Conservative: sirolimus (6-month-long, stopped for cardiac surgery procedure)	Redo therapy for recurrent anemia
	13 / F	Shoulder vascular malformation (excised)	IDA Positive heme occult stools	Iron replacement therapy	Abdominal Angio CT: intestinal vascular malformations Upper, lower GI and capsule recommended but not completed	No	Conservative: sirolimus	Resolution of anemia
	17 / F	Scalp venous malformation	Normocytic anemia	Upper GI: bleeding esophageal and gastric lesions VCE	No delay	(T) Upon arrival. (F) Small bowel lesions	Conservative: sirolimus (6-month-long, stopped for infection)	Resumed therapy and resolution of bleeding and anemia
[45]	10 / F	Previous diagnosis of BRBNS	Low back pain and neurologic deficit	MRI: dorsal L4-L5 epidural lesion	No delay	ND	Surgical cauterization	ND
Present case	15 / F	Venous malformation of the left paravertebral region (exeresis at birth)	Chronic IDA	CT scan and isotope scan with technetium-99m-pertechnetate: normal	Upper GI: strawberry-like mucosal polypoid lesions in the stomach. (D) 4 years	(T) With other endoscopic evaluations (F) Ten hemangiomas distributed in the small bowel	Conservative: sirolimus	Healthy (1 year)

Table 1 resumes pediatric cases (age 0-18 years) of BRBNS reported in the Literature in the last five years. The review shows how lesion location attests to the variability of the clinical picture. Additionally, GI lesions are more prone to underhand symptoms leading to diagnostic delays. Medical treatment with Sirolimus seems promising, especially when other therapies would be too aggressive or fail [26-45]. In our case, a "dominant lesion" was detected at birth, as it generally happens, but it was resected before the diagnostic definition. When the patient came to our attention, there was initially a misreported clinical history, and BRBNS was not suspected. Isoldi et al. reported that most patients in their series of 18 BRBNS became transfusion-dependent during pediatric age with a mean diagnostic delay (presentation to diagnosis) of 2.2 years [46].

This case and the literature review support the idea that pediatric patients with suspected BRBNS should be investigated by upper and lower GI endoscopy, including VCE [16,45-47]. VCE may produce a kind of "map" that detects digestive lesions beyond the stomach and enables their clear definition and localization. The capsule is either placed endoscopically (in patients < 5 years of age) or swallowed by the child; in the latter case, it allows for avoiding deep sedation [48,49]. It has the advantage of limiting diagnostic invasiveness, although careful patient selection is mandatory to prevent complications (e.g., considering patients' age and possible intestinal stenosis). It is also a valuable tool for monitoring the effects of therapy.

Conclusion

In different approaches have been proposed for managing pediatric patients with BRBNS. The evaluation of the child in centers dedicated to pediatric care with gastroenterological, surgical, and endoscopic expertise is of uttermost importance, as well as the involvement of a multidisciplinary team to manage associated problems. A complete endoscopic evaluation (including VCE), as established in SIGENP guidelines, is mandatory in case of anemia and suspected obscure mid gut bleeding [48]. Efforts are required to reduce the delay between symptom onset and diagnosis. The treatment should avoid Substitute demolition with aggressive approaches, especially for the possibility of recurrences. Future studies should focus on the possibility of applying innovative imaging modalities (such as 3d reconstructions) for both the first diagnosis and the follow-up and on the consolidation of conservative medical strategies (e.g., Sirolimus).

Author Contribution

Conceptualization, G.P.; methodology, G.P., G.L., F.D., U.M.P; Investigation, G.P., G.L., F.D. C.A.; Original draft preparation,G.P., G.L.; writing-review and editing, G.P., F.D. V.B.;Supervision, G.P. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Institutional Review Board Statement

Data were retrospectively evaluated according to the principles of the Declaration of Helsinki as revised in 2008. The reservedness of the collected information was ensured according to Regulation (EU)/2016/679 GDPR (Regulation (EU) 2016/679), Legislative Decree n.101/18.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Data supporting reported results are archived in the first Author's personal datasets.

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